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EARLY ADVERSE EVENTS OF PELVIC RADIOTHERAPY

Dr. Ahmed Abdul Jabbar Alaskari*

Clinical Oncologist, Kerbala, Iraq.

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***Corresponding Author**
Dr. Ahmed Abdul Jabbar Alaskari
Clinical Oncologist, Kerbala, Iraq.

INTRODUCTION

radiotherapy is used with or without chemotherapy to treat malignancies in the pelvis that occur in gynecologic, genitourinary, and gastrointestinal organs. Radiation can cause functional effects on GIT organs including the rectum, anus and small bowel which is (the most sensitive organs in the pelvis can be affected), a pathologic and clinical effects that can result during radiotherapy treatment and shortly thereafter.[1]

Radiation produce its effects through both direct action (one– third) and indirect action (two–thirds). Direct action refers to direct damage to DNA, whereas indirect action is mediated through free radicals produced through ionization of H2O.[2]

The window of safety is narrow or perhaps nonexistent because the doses that cause injury are very close to the doses needed for therapy. Cells are most sensitive to radiation during the G2 and M stages of mitotic division; therefore, the most rapidly dividing cells are the most radiosensitive.[3]

Radiation-induced injury to small and large intestine is best described in 2 ways. Acute injury and chronic injury; Acute intestinal injury induced by ionizing radiation is directly related to the dose and frequency at which radiation is given. The effects of ionizing radiation on the intestinal mucosa in the acute setting are generally ascribed to inhibition of epithelial cell mitosis deep within the mucosal crypts. Loss of mucosal surface leads not only to loss of water, protein, and electrolytes but also to loss of the mucosal protective barrier. Therefore, the gut is rendered permeable to bacteria and other antigens, which may exacerbate the inflammatory response and perhaps lead to bacteremia. In addition to its effects on the mucosa, radiation affects bowel motility.[4]

Chronic injury: is an indolent process that can arise 3 months after therapy completion or up to 30 years later. In addition to the acute cellular toxicity, radiation causes a progressive, obliterative arteritis and submucosal fibrosis. Transmural injury of the bowel wall can lead to a progressive vasculitis, thrombosis, and, ultimately, varying degrees of ischemia and necrosis. This process may lead to narrowing of the bowel lumen and eventual obstruction. The effects of chronic radiation are primarily related to the total dose of radiation received as well as the total volume of tissue irradiated. One must keep in mind that patients with chronic radiation changes often develop dense intra-abdominal adhesions after radiation exposure and have very little free domain in their abdomen. Localized perforations may occur, and an elevated awareness is required to avoid missing a life-threatening diagnosis. On the other hand, exploratory surgery for chronic radiation injury should be approached with caution, as surgery carries significant morbidity and mortality in this population of patients.[15]

Symptoms can appear early, within hours of the first treatment session; very shortly after therapy; or months to years after the treatment has ended. Early presentation In most situations, patients experience acute symptoms 2-3 weeks into the treatment. Symptoms usually resolve in 2-6 months. Symptoms tend to be self-limited and mild in severity, requiring predominantly symptomatic therapy. The correlation between the severity of mucosal damage and the severity of symptoms appears to be poor. Symptoms include the following: Anorexia, Nausea (More frequent with upper abdominal radiation), Vomiting (More frequent with upper abdominal radiation), Abdominal cramps (Consequence usually of small intestinal involvement), Diarrhea (More often observed as a consequence of pelvic irradiation), mucoid rectal discharge (As a result of rectal involvement) and Rectal bleeding (As a result of rectal involvement). Any patient with a history of radiation to the abdomen or pelvis presenting with GI complaints should raise suspicion for radiation-related toxicity until proved otherwise.[16]

in the UK, 12 000 individuals are treated with radical radiotherapy for pelvic cancer annually, mostly with curative intent. During their five or six week course of treatment, approximately 80% of patients will develop gastrointestinal symptoms which are partly caused by acute gastrointestinal inflammation and affecting quality of life.[5]

Despite the advances in the field of radiation oncology, radiation enteropathy continues to be a major obstacle to the radiocurability of abdominal and pelvic tumors. The incidence of

bowel-related toxicity after radiotherapy treatment is quite variable. Much of this variability is dependent on treatment dosing schedules and technique, which vary with cancer type.[16]

Numerous grading systems are utilized in the literature to assess bowel toxicity from radiotherapy. the National Cancer Institute has evolved the Common Terminology Criteria for Adverse Events (CTCAE) v.3.0, formerly Common Toxicity Criteria (CTC), to represent a more global assessment of cancer treatment–related toxicity. (CTCAE) is a descriptive terminology which can be utilized for Adverse Events (AE) reporting. A grading (severity) scale is provided for each AE term. Grade refers to the severity of the adverse events. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each adverse events based on this general guideline: Grade 1(Mild adverse events), Grade 2 (Moderate adverse events), Grade 3 (Severe adverse events), Grade 4(Life-threatening or disabling adverse events), Grade 5 (Death related to adverse events).[6]

Acute enteritis secondary to radiation therapy is usually a self-limiting process treated conservatively with dietary changes and antidiarrheal medications. Mild intermittent symptoms of chronic enteritis are managed with a low-residue diet, stool softeners, and loperamide (Imodium). Normal portions of foods with moderate-to-high fiber content can exacerbate symptoms of chronic radiation enteritis. Lactose intolerance is common following radiation, although patients may tolerate small portions of dairy products.[7]

The new radiotherapy modality like conformal (Three dimensional) treatment planning techniques had been widely used and it carry good tumor local control with minimum acute and late radiation toxicity because the radiotherapy treatment field size will be smaller than that of conventional treatment that it take the shape of tumor by the help of CT scan while in conventional radiotherapy treatment it depend on x-rays and the radiotherapy treatment fields are much larger than the size of tumor so the radiotherapy toxicity will be more in this type of treatment.[18]

Pretreatment barium contrast studies is of benefit in radiotherapy treatment to avoid intestine because it can determine how much of the small intestine is in the pelvis. Filling the urinary bladder may push the small bowel away from the pelvis. Body positioning in the prone position, decubitus, or the Trendelenburg position may be helpful. A special table with a central cavity, which allows the bowel loops to drop away from the target tissue, has been described, all these measure will help to decrease radiation toxicity to the GIT.[3]

A number of innovative prophylactic surgical therapies have been proposed, and include the following: Biodegradable mesh slings, Sodium chloride–filled tissue expanders, Inflatable prosthesis, Abdomino-pelvic omentopexy and Suturing the bladder to the sacrum. The concept in these surgical procedures is to keep the intestines away from the radiotherapy treatment fields and so the toxicity will be minimized.[8]

Pharmacologic agents include antioxidants in the form of vitamin E and vitamin E-like compounds, as well as the lazaroids (i.e. 21-amino steroids) and more recently octreotide. Although nonsteroidal anti-inflammatory drugs have shown some promise in animal studies, the results with a prostaglandin analogue, misoprostol, have been less than satisfactory. Sucralfate therapy in doses varying from 1 g every 4-6 hours during treatment and for another 3-4 weeks thereafter has been shown effective during pelvic irradiation.[9]

AIM OF THE STUDY

The aim of this study is to identify the early adverse events of GIT toxicity due to pelvic radiotherapy and identifying risk factors and the best way to minimize or prevent them.

PATIENTS AND METHODS

A cross-sectional study that included thirty patients attended to the Al-Amal national hospital for cancer management in Baghdad in 2012-2013, these patients already diagnosed with different types cancers (Uterine cancer, cervical cancer, vulvar cancer, rectal cancer, anal cancer and prostate cancer) in which they need for pelvic radiotherapy during their course of management.

patients included 12 males and 18 females, their ages ranged from 25-73 years. All patients had histopathological report and complete work up, and some of them are treated previously with surgery and either or chemotherapy.

All parameters estimated depended only on history which based on a questionnaire about the symptoms that related to the GIT radiation toxicity which include (anorexia, nausea, vomiting, diarrhea, pain, constipation, and bleeding per rectum) and submitted on Common Terminology Criteria for Adverse Events v3.0; in which it classified each adverse events according its severity and the need for treatment, and it range from grade 0 (no symptom) to grade 5 (death related to symptom) as described in this table.

		Grades				
Adverse event	**Short name**	**1**	**2**	**3**	**4**	**5**
Anorexia	Anorexia	Loss of appetite without Alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	death
Nausea	Nausea	Loss of appetite without Alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening Consequences	Death
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening Consequences	Death
Pain	Pain	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	-
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon	Death
Diarrhoea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
Bleeding per rectum	Bleeding per rectum	Mild, intervention not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

Timing of history taking is during radiotherapy course (at least after the 7th fraction), all patient treated with radiation dose of 45-70 Gy in 25 - 35 fractions with one fraction/day and 5 fraction/week.

RESULTS

In our study thirty patients with pelvic organ cancers who are treated by radiotherapy are evaluated regarding to the early GIT symptoms (adverse events) related to the pelvic radiotherapy complication which are include (anorexia, nausea, vomiting, diarrhea, constipation and blood or mucous in stool).

Majority of patients in our study are with symptoms associated with GIT toxicity as shown in table (1).

Table 1: patient's gender distribution in the studied group.

Presence of adverse events	No. of patient	percentage
Symptomatic	24	80%
Asymptomatic	6	20%
Total	30	100%

In this study the total number of adverse events are 96 adverse events related to the pelvic radiotherapy toxicity we found that the incidence of GIT adverse event is about 2.3 for each patient who treated by pelvic radiotherapy as shown in table (2).

Table 2: Adverse events incidence in the studied group.

No. of pt	No. of adverse events	(adverse event / patient)
30	69	2.3

We found that the most common early adverse events is pain (56.6%) and the least one is the blood in stool (0%) which shown in table (3).

Table 3: Early adverse events in pelvic radiotherapy.

Adverse event	no. of patients who had adverse events	%
Pain	17	56.6
Anorexia	14	46.6
Nausea	12	40
Diarrhea	11	36.7
Mucous in stool	6	20
Constipation	5	16.7
Vomiting	4	13.3
Blood in stool	0	0

Most of the symptomatic patient are of Grade 1 (70%) and the remaining are of Grade 2 (30%), while the higher grade (grade 3,4 and 5) are not seen in our study, table (4).

Table 4: Adverse events grades in the studied group.

Grade	No. of patient	percentage
Grade 1	21	70%
Grade 2	9	30%
Grade 3	0	0
Grade 4	0	0
Grade 5	0	0

Gender distribution in our study and its relation to the incidence of adverse events are shown in table (5).

Table 5: Gender distribution and its relation to the incidence of adverse events in the studied group.

Gender	No. of patient	percentage	No. of adverse events	Adverse event / patient
Female	18	60%	45	2.4
Male	12	40%	24	2

Age of patients in this study are divided into two groups, above and below 50 years and the results are shown the majority of the patient are above 50 years (80%), we also calculate the adverse event incidence in each group as shown in the table (6).

Table 6: Age distribution and relation to the incidence of adverse events in the studied group.

Age	No. of patient	Percentage	No. of adverse event	Adverse event/patient
Above 50 years	24	80%	55	2.3
Below 50 years	6	20%	15	2.5

The type of planning for the radiotherapy treatment and its association with the Adverse events incidence are shown in the table (7), in which their were 14 patients treated by conventional radiotherapy modality (2D) and we found the no. of adverse events are high in this group, while the other group (16 patients) treated by conformal radiotherapy modality (3D) and we found the adverse incidence of the adverse events are much less as shown in the table (7).

Table 7: Treatment planning modality distributions and its relation to the incidence of adverse events in the studied group.

Plan	No. of patients	%	No. of adverse events	Adverse event /patient
2D	14	46.6	44	3.1
3D	16	53.4	19	1.1

We also find that not only the incidence of the radiotherapy adverse events are increase in the conventional radiotherapy treatment modality but also its grade, that 20 patients who treated by conventional radiotherapy modality (2D) were had grade 2 adverse events, while patients who treated by the conformal radiotherapy modality (3D) only 1 patient had adverse events of grade 2 as shown in table (8).

Table 8: Association between radiotherapy treatment modality and grade of the adverse events.

Plan	No. adverse event	No. of Grade 1 adverse events	Grade 1	No. of Grade 2 adverse events	Grade 2
2D	44	24	54.5%	20	45.5%
3D	26	25	96.1%	1	3.9%

DISCUSSION

In our study we found that most of the patients (80%) had adverse events related to the GIT toxicity from the pelvic radiation. GIT is anatomically close related to the pelvic organ that make it or the most parts of this system in the treatment fields of radiotherapy, this fact is consistent with J. Andreyev; who stated that during the course of radiotherapy treatment, approximately 80% of patients will develop gastrointestinal symptoms which are partly caused by acute gastrointestinal inflammation.[5]

Also we found that the incidence of GIT adverse event is about 2.3 adverse events for each patient who treated by pelvic radiotherapy ,this result is consistent with H. Jervoise et al who stated that More than one-half of the patients had more than one GI diagnosis contributing to their symptoms after pelvic RT.[13]

Clinically in this study we found that early GIT toxicity adverse events that can occur in the radiotherapy treatment were include: anorexia, nausea, vomiting, diarrhea, pain, constipation, mucus in the stool. This fact was consistent with Rajeev Vasudeva et al, William Small et al and J. Andreyev.[3,1,5]

Moreover, according to the result of this study most of the symptomatic patients are of low grade; Grade 1 (70%) and the remaining are of Grade 2 (30%), while the higher grade (grade 3,4 and 5) are not seen in our study, in spite of the toxicity effect of radiotherapy to the GIT, the normal cells can increase its replications and renewal the tissue which damaged by radiation and retain this tissue to its normal function, and so decreasing the severity (grade) of adverse events that caused by radiotherapy, this results are consistent with Rajeev Vasudeva et al and Frank J Sullivan et al.[3,10]

In our study we compare the incidence of adverse event according to the gender, we found that the incidence of adverse events in both gender are approximately same (about 2 adverse event per patient), this fact is in consistent with Tait DM et al and Rajeev Vasudeva et al.[14,3]

Regarding to the Age of patients in our study patient age range (27-90 years) we found the majority of patient are above 50 years (80%) this fact is in consistent with result of Cancer Statistics Registrations of England in which the more than half of the cancer patients are in age above 50 years.[12]

We also submitted adverse event data for each age group(above and below 50 years) and we found the adverse event incidence of both groups are approximately same, hence the effect of patient's age on the probability of pelvic radiotherapy complication is not significant, this fact is in consistent with Tait DM et al, J. Andreyev and Rajeev Vasudeva et al.[14,5,3]

In our study we found that there is increase in incidence of symptoms and its grade when patient is treated by conventional radiotherapy (2D) rather than conformal radiotherapy (3D), in our study we found the incidence of adverse events in conventional radiotherapy is two times more than that in conformal radiotherapy, this result are due to that in conformal radiotherapy the treatment field size is concentrate on the shape of tumor and so the normal organ tissue volume will be less involved by radiation, in addition in conformal radiotherapy it can calculate who much the normal organ receive radiation and so it can keep the GIT within the normal limit of radiation exposure, so by these benefits of conformal radiotherapy the GIT radiation toxicity is much less than that in conventional radiotherapy, these results are consistent with Diana M. et al, Rajeev Vasudeva, Gregory D. Kennedy et al and J. Andreyev.[11,3,4,5,18]

CONCLUSIONS

From the present study we can conclude the following.

1. Most of the patient with pelvic organ cancer who treated by radiotherapy are susceptible for developing of GIT complications during the course of treatment (80%).
2. Most of GIT complications are of low grade (70% grade1 and 30% grade 2).
3. All patients with GIT complications in our study didn't cause treatment interruption and they need only symptomatic treatment.
3. Most common presenting symptoms is pain (56.6%) and the least one is the blood in stool (0%).
4. Age and gender of patient are not associated with increasing risk of GIT toxicity.
5. Radiotherapy treatment modality are important factor to avoid or decrease the risk of GIT toxicity, in our study the conformal radiotherapy is better than conventional radiotherapy.

Recommendations

1. Using conformal radiotherapy treatment modality rather than conventional one.
2. Further studies regarding chronic adverse event of GIT radiation toxicity.

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